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EXAMINER	
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ART UNIT	PAPER NUMBER
1624	17

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/805,296	Applicant(s) EFIMOV ET AL.	
	Examiner Thomas McKenzie Ph.D.	Art Unit 1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *97-129* is/are pending in the application.

4a) Of the above claim(s) *97-107 and 114-129* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *108-113* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1)☐ Notice of References Cited (PTO-892)
2)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3)☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 4,5,P,$16
4)☐ Interview Summary (PTO-413) Paper No(s). _____ .
5)☐ Notice of Informal Patent Application (PTO-152)
6)☐ Other:

DETAILED ACTION

1. This action is in response to an election filed on 2/10/03. There are thirty-three claims pending and six under consideration. Claims 108-113 are compound claims. This is the first action on the merits. The application concerns some nucleobase compounds linked to a 4-hydroxyproline and uses thereof.

Election/Restrictions

2. Applicant's election with traverse of Group V in Paper No. 14 is acknowledged. The traversal is on the ground(s) that there is common subject matter and no search burden is present. This is not found persuasive because according to MPEP §803 "For purposes of the initial requirement, a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That prima facie showing may be rebutted by appropriate showings or evidence by the applicant." Applicants pointed to no errors in the Examiners analysis of the classification of the different inventions. Thus, there is no common subject matter. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 97-107 and 114-129 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there

being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 14.

4. Objection is made to claims 108-113 as containing non-elected subject matter. The claimed compounds, compositions, and methods that employ them present a variable core. Formula of claim 108 contains compounds drawn to the non-elected inventions to the extent it reads on compounds other than B^2 = a purine or a pyrimidine.

Information Disclosure Statement

5. The information disclosure statement filed 9/5/01 (paper #4) fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. The Examiner has ordered a search made for these missing documents but, so far, that search has not been fruitful.

Specification

6. The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the

applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973). The issue concerning the PCT applications and the meaning of "non-naturally occurring nucleobase" is discussed below.

7. The possible use of the trademarks Cy3 and Cy5 is discussed below. They should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks.

Title

8. The title of the invention is not descriptive of the elected invention. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: adding "Purine and Pyrimidine" before the word "Oligonucleotide".

Abstract

9. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract is too generic. Examiner suggests claim 108, including the figure.

Claim Rejections - 35 USC § 112

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 108-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The structure of claim 108, which corresponds to formula **(XII)** on page 54 contains a negative charge on one of the oxygen atoms bonded to phosphorus. No positive counter ion is shown in the claim or on page 54. The variable n is "1 or greater". Therefore an infinite number of negative charges are possible. What is intended here?

11. Claims 108-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject

matter which applicant regards as the invention. The structure of claim 108, which corresponds to formula **(XII)** on page 54 contains unsatisfied valences on the nitrogen containing variable T and the carbon atom containing variables R^{12} and R^{13}. These are trivalent and quadravalent atoms respectively, yet only 2 and 3 radicals are shown bonded to them. The Examiner understands that when n is greater than 1, then a bond is intended between these two atoms in adjacent monomer units. However, when n = 1 what is attached? When n is greater than 1 what is attached to the two terminal atoms? Could a cyclic molecule be intended where these two terminal atoms are bonded together?

12. Claims 108-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The elected subject matter of claim 108 includes radical B^1 selected from "a non-naturally occurring nucleobase, an aromatic moiety, a DNA intercalator, a nucleobase-binding group, a heterocyclic moiety, or a reporter group". These six terms are indefinite because it is unclear what are the structures of the claimed radicals.

Applicants define "non-naturally occurring nucleobase" in lines 5-17, page 14 of the specification. The definition uses open language "such as" and "can be". Applicants list a number of bases not found in natural nucleosides in lines 9-14,

page 14. What bases in addition to these are being claimed? The passage cited incorporates by reference two US Patents and four PCT applications. While US Patents may be incorporated by reference, PCT applications may not. Search of the two US Patents, reveals no usage of the phrase "non-naturally occurring nucleobase". In lines 18-23, column 5 of US Patent 6,150,510 there is a definition of "unnatural bases". The definition also uses open language "such as, for example". All of the specific radical listed in the passage cited appear to be incorporated into Applicants' list. What additional radicals are being incorporated from US Patent 6,150,510?

13. The Examiner can find no definition of either "aromatic moiety" or "heterocyclic moiety" in the specification. Aromatic is a chemical property. It refers to compounds which conform to Huckel's rule and contain 6, 10, 14, 18 etc π electrons in a ring system. It could refer to all carbon rings or to rings containing non-carbon atoms. Does "aromatic moiety" include heteroaryl compounds like pyridine and purine or are only hydrocarbons intended? Cyclopentadiene anion, cyclooctatetrene dianion, cyclopropenyl cation, and cycloheptatrienyl cation are considered by some to be aromatic hydrocarbons. Are these intended?

14. There are inconsistent and differing uses of the word heterocycle in the chemical arts. The widely used textbook “Organic Chemistry” by Fessenden says

on page 451 that the compounds must be aromatic but that any and all of the atoms in the ring may be selected from the entire periodic table. The widely used "Condensed Chemical Dictionary" also implies that a heterocycle must be aromatic but that only 5 or 6 membered ring compounds with sulfur or nitrogen, not every possible atom are included in the meaning of 'heterocycle". The less widely used textbook "Introduction to Organic Chemistry" by Streitwieser on page 1061 defines 'heterocycles" as both aromatic and nonaromatic. It further implies that the nitrogen, oxygen, and sulfur atoms are commonly meant and that any size ring falls under the sense of the word. The US Patent Office in the classification definitions does not consider a ring consisting of carbon and phosphorus to be a heterocycle but Hackh's (Chemical Dictionary) lists phosphorus as one of six permissible heteroatoms. Does heterocycle refer only to aromatic compounds or are saturated compounds like piperidine also included? Is a ring containing carbon and phosphorus a "heterocyclic moiety"? Is it only 5 and 6-membered ring compounds or is homopiperazine included? Are oxygen containing rings included? How about chlorine or boron?

15. In lines 3-8, page 16 Applicants define "intercalator" as anything "that can bind a nucleic acid molecule". DNA is a type of nucleic acid molecule but of course is not the only type. Are all "intercalator" molecules DNA intercalors" or

just some of them? How large must the associate constant be for an intercalator to be considered bound to the DNA? Does this apply only to flat molecules, which can interleaf into the major and minor groves of DNA or are molecules like histones that bind purely through charge also included? In lines 4-8 Applicants list some possibilities using open terms, "non-limiting". What else is intended? The molecule quinoline is listed in the singular but dihydroquinones are plural. What does that imply? Are only para dihydroquinones intended or are ortho-dihydroquinones also included? Are these dihydrobenzoquinones or could they be napthtoquinone and anthroquinone also? Must they intercalate all DNA molecules or just some?

16. The Examiner can find no definition of "a nucleobase-binding group" in the specification although "nucleobase" is defined in lines 5-7, page 14. Is this intended? Applicants do not assert and the Examiner can find no evidence that "a nucleobase-binding group" is an art-recognized term. The definition of nucleobase includes "non-naturally occurring nucleobase" which is discussed above.

17. Applicants define "reporter group" in lines 9-18, page 16 again using open language. We are taught it is any group "directly or indirectly detectable". Detectable how and with what sensitivity? What does indirectly detectable mean? The list of specific molecules found in lines 10-18, page 16 is exactly that,

molecules, not the univalent radical required of B^1. Both **CY3** DIRECT® and **CY5** DIRECT® are registered trademarks of AMERSHAM BIOSCIENCES for fluorescent dyes for labeling nucleotides and proteins for scientific and research use. Is this what is intended in line 14, page 16? If not, what?

18. Claims 108-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The structure of formula I(c) in claim 108 contains a nitrogen atom with only two satisfied valences. What else is attached to this atom?

19. Claims 108-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the final section of claim 108 there is a definition of radicals R^{18} to R^{21}. Where are these radicals found in the formula of the claim?

20. In addition, the limitations " a chelator, a linker, a peptide, a protein, a carbohydrate, a lipid, a steroid, a nucleotide or oligonucleotide, or a soluble or insoluble polymer" are indefinite because they fail to specify the structures of the claimed radicals. The Examiner suggests deleting the definitions of radicals R^{18} to R^{21}.

21. Claims 109-113 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "[t]he compound" in claim 109 means that the additional "oligonucleotide analogue monomer" must be covalently attached to the formula of claim 108. Where is this attachment to occur? Is it attached only at the unsatisfied valences on the nitrogen containing variable T and the carbon atom containing variables R^{12} and R^{13} discussed above? Could it be at the unprotected nitrogen atoms? Could it be anywhere in the molecule?

22. Claim 109 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "oligonucleotide analogue monomers" is indefinite. Nowhere in the specification is this term defined *verbatim*. What are the structures of these radicals? In lines 18-26, page 13 ""monomers" of nucleic acid analog" as described as "nucleobase, or a derivative or analogue thereof". What derivatives and which analogues? The issue of nucleobase was discussed above. A derivative is the result of a reaction upon an organic molecule. Since we do not know the reagents or the conditions of these reactions, there is no way of determining the structures of the claimed

"derivatives". In line 1, page 18 Applicants have the title "Oligonucleotide Analogues" followed by the structures of monomers **I** through **V**. Is this what is intended?

23. Claims 110 and 111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "the compound of claim 1" and "claim 1 monomer" are indefinite because claim 1 is no longer pending. Now cancelled claim 1 is drawn to compounds of formula **I** on page 18. The Examiner suggests using this structure in the two claims.

24. Claims 110 and 111 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrases "a phosphono peptide nucleic acid monomer" is indefinite. Again, nowhere in the specification is this term defined *verbatim*. What is the structure of this radical? In lines 24-27, page 1 Applicants introduce the abbreviation "pPNAs" for phosphono peptide nucleic acid. In lines 16-19, page 12, Applicants define "a phosphono peptide nucleic acid" but fail to specify if this is a monomer. They use open language "comprising" "such as". In lines 23-26, page 13, Applicants define "monomer unit of a peptide nucleic acid" but fail to specify if this is a phosphorus containing

peptide. The definition includes "nucleobase (or nucleobase analogue, nucleobase-binding unit, ligand, intercalator, reporter group or label)". The indefiniteness of these terms has been discussed above. The nucleobase "is covalently attached to an amino acid or amino acid derivative or analog". Does amino acid refer to the twenty naturally occurring amino acids, which are coded for in DNA, or are all compounds containing any acid and amine group intended? The issue of derivative or analogue was discussed above. The three structures **II-IV**, pages 20, 22, and 24 are described as hydroxyproline and aryl phosphono peptide nucleic acid monomers. Is this what is meant? The Examiner understands that hydroxyproline is an amino acid, which may be incorporated into a peptide, but itself is not a peptide. An aryl group is not a peptide but structure IV apparently may contain additional peptides in radicals G and E. The Examiner suggests using structures **II-IV**, if that is what is intended.

25. Claim 112 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The indefiniteness of "nuclebase" generally as including non-naturally occurring nucelobases was discussed above.

26. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 108-113 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for compounds with a hydrogen attached to the terminal atom N(T) and an amino (NH_2) group attached to the terminal atom $C(R^{12}R^{13})$, does not reasonably provide enablement for any other groups attached to these positions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The issue of the chemical impossibility of Applicants formula in claim 108 was discussed above.

"The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. a) Synthesis of compounds of formula (**XII**) would require preparation of the individual monomers and repeated coupling, a moderate degree of experimentation. b) The direction concerning the synthesis of the compound (XII) on page 54, which corresponds to the formula of the claim, is taught in lines

16-18, page 57. In lines 16-17, page 62 we are taught that (**XII**) may be made from (**VIII**). Working Examples 13 and 14 on pages 113-115 teach end capping with acetic anhydride in lines 26-28, page 113 and resin cleavage with concentrated ammonium hydroxide in the passage spanning line 32, page 113 to line 1, page 114. The acetic anhydride will react with any free hydroxylproline group, of which formula (**XII**) has none. The ammonia will cleave the resin-bound acid producing a primary amide $C(O)NH_2$ and will cleave the amine protecting group off the terminal "a phosphono peptide nucleic acid" (pPNA) producing a primary amine. c) There are two working example of a synthesis compound of formula (**XII**) discussed above. d) The nature of the invention is chemical synthesis, which involves chemical reactions. e) The state of the nucleotide synthesis art is nicely summarized in the references mentioned in lines 3-16, page 32. f) The artisan using Applicants invention to prepare compounds would be a process chemist or pilot plant operator with a BS degree in chemistry and several years of experience. g) Chemical reactions are well-known to be unpredictable, *In re Marzocchi*, 169 USPQ 367, *In re Fisher*, 166 USPQ 18. h) The breadth of the claims includes all of the millions of various R, B^1, B^2, $A^{2,}$ and T-groups of formulas (XII) and the unlimited size of the claimed oligomers. Thus, the claims are broad.

27. Claims 108-113 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making compound of formula given in claim 108 with n greater than 1, does not reasonably provide enablement for making such compounds with n = 1. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. Apart from the issue of what is attached to the ends of the compounds, the synthesis of the compound (**XII**) on page 54, which corresponds to the formula of the claim, is taught in lines 16-18, page 57. In that passage we are taught that oligomers may be made. Oligomers require more than one monomer. In lines 16-17, page 62 we are taught that (**XII**) may be made from (**VIII**), which in turn is pictured on page 25. Compound (**VIII**) contains no bond between the phosphorus atom and the oxygen atom on the proline ring. Compound (**VIII**) is quite different that compound (**XII**). If that bond is formed between phosphorus and oxygen employing two molecules of (**VIII**), then a compound resembling but not identical to (**XII**) results. However, that molecule must have n = 2. How is the compound claimed with n = 1 to be made?

28. Claims 108-113 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The issue of the charge on oxygen was discussed above. It would violate the laws of chemistry to isolate such a compound. If the compound cannot be isolated, then how is it to be used?

29. Claims 109-111 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for insertion of a further oligonucleotide analogue monomer between the phosphorus atom and the oxygen on the proline ring, does not reasonably provide enablement for insertion of a further oligonucleotide analogue monomer elsewhere. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection were discussed above as were Applicants' teachings. Applicants' synthetic process concerns repetitive phosphorus oxygen coupling. Do Applicants possess a method of adding a further oligonucleotide analogue monomer to R^{14}, say as covered by the claim language "further comprising"?

Conclusion

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas McKenzie Ph.D. whose telephone number is (703) 308-9806. The examiner can normally be reached on 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (703) 308-4716. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 746-3152 for regular communications and (703) 308-4556 for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Mukund J. Shah

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

TCMcK
April 15, 2003